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ORIGINAL ARTICLE

Protocol for direct reporting of awareness in maternity patients (DREAMY): a prospective, multicentre cohort study of accidental awareness during general anaesthesia

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ABSTRACT

Background: Accidental awareness during general anaesthesia (AAGA) is a complex and rare outcome to investigate in surgical patient populations, particularly obstetric patients. We report the protocol of the Direct Reporting of Awareness in Maternity patients (DREAMY) study, illustrating how the research was designed to address practical and methodological challenges for investigating AAGA in an obstetric cohort.

Methods: This is the trial protocol of a prospective, multicentre cohort study of patients undergoing obstetric surgery under general anaesthesia. Accidental awareness during general anaesthesia will be detected using three repetitions of standardised direct questioning over 30 days, with responses indicating memories during general anaesthesia verified using structured interviews. Reports will be adjudicated, then classified, in accordance with pre-defined and pre-validated structures, including the Michigan Awareness Classification tool. Quantitative data will be collected on general anaesthesia conduct for all participants. This descriptive study is being conducted in England and aims to recruit a minimum of 2015 patients.

Results: The DREAMY study was prospectively registered (ClinicalTrials.gov Identifier: NCT03100396) and ethical approval granted. Participant recruitment began in May 2017 and one year follow up concluded in August 2019. Publication of the results is anticipated in 2020.

Conclusions: The DREAMY study will provide data on incidence, experience and implications of AAGA for obstetric patients, using a robust methodology that will reliably detect and translate subjective AAGA reports into objective outcomes. In addition, the study is expected to improve vigilance for AAGA in participating hospitals and encourage adoption of recommendations for support of patients experiencing AAGA.

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Keywords: Awareness; Consciousness; Obstetric surgery; Perioperative complications; Research protocol

Background

The 5th National Audit Project in the UK and Ireland (NAP5)¹ was the largest study to investigate accidental awareness during general anaesthesia (AAGA). The NAP5 methodology combined national surveillance for spontaneous patient reports of AAGA and a parallel snapshot survey of general anaesthetic activity.² Obstet-

ric patients undergoing caesarean delivery were markedly over-represented, constituting almost 10% of all NAP5 AAGA reports but only 0.8% of general anaesthetic activity. Importantly, NAP5 adopted a different approach to study design from most previous investigations, relying solely upon descriptions spontaneously reported by patients to clinicians rather than asking patients directly about their memories. Whilst it may be argued that NAP5 was successful in detecting the most clinically relevant AAGA experiences,³ it is not known how many cases of AAGA were missed due to anxiety or lack of opportunity or motivation among patients to declare their experience.

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A more common methodological approach to detect AAGA is to screen patients using a standardised interview format, typically based upon a set of questions termed the Brice interview.⁴ The Brice interview questions provoke patients to recall their memories of the induction and emergence stages of a general anaesthetic, including anything that may have occurred in between. Studies using such direct questioning consistently estimate the incidence of AAGA at 1–2:1000.^{5–11} In contrast, NAP5 estimated the incidence of AAGA to be far lower at ~1:19 000 general anaesthetics, albeit with considerable context-dependent variation: ~1:8000 when neuromuscular blocking drugs (NMBDs) were used compared with ~1:136 000 without NMBDs and ~1:670 for caesarean delivery.

Obstetric general anaesthesia has multiple risk factors for AAGA, for example the universal use of NMBDs, rapid sequence induction, a high incidence of difficult airway management¹² and emergency surgery. Previous attempts to quantify AAGA in obstetric patients using the Brice interview have indicated a disproportionately high risk, ranging from an estimated incidence of 1:110 during the 1980s,¹³ to 1:382 in the mid-2000s.¹⁴ These studies involved results with wide confidence intervals and a lack of consistent AAGA classification, and are difficult to translate to current anaesthetic practice given recent changes in anaesthetic management for obstetric general anaesthesia.¹⁵ Brice interviews were used by Paech et al., however the findings were limited by a relatively small sample size (n=763) and a lack of verification of AAGA reports beyond one or two brief interviews.¹⁴

The aim of the Direct Reporting of Awareness in Maternity patients (DREAMY) study is to describe the epidemiology of AAGA in a cohort of adult patients undergoing obstetric surgery, describing the incidence, nature of experiences, risk factors and implications of AAGA. The study aims to fulfil research implications from NAP5 in relation to AAGA in the obstetric population. These implications were to “define the incidence of AAGA as identified by the Brice questionnaire” (Research Implication 16.6) and “explore whether factors make obstetric patients more likely to report episodes of AAGA than the non-obstetric population” (Research Implication 16.7).¹⁶ The primary objective is to describe the incidence of different classifications of AAGA, identified using direct questioning following obstetric surgery. Secondary objectives are to: 1. Describe the characteristics of the patient population undergoing obstetric surgery under general anaesthesia. 2. Investigate the conduct of general anaesthesia for obstetric surgery, including pharmacological and airway management, workforce considerations, and the risk of any complications. 3. Describe the psychological implications of AAGA using a post-traumatic stress disorder symptom checklist follow up over 12 months and any

prognostic factors for this. 4. Investigate the association between risk of AAGA and patient or anaesthetic characteristics. 5. Investigate the association between dreaming during general anaesthetic and patient or anaesthetic characteristics.

Methods

Ethical approval for this study was granted by the UK National Research Ethics Service (London Fulham Committee; REC reference 17/LO/0071). Trial registration was obtained prospectively (ClinicalTrials.gov Identifier: NCT03100396). This protocol is reported in accordance with the STROBE statement for reporting epidemiological observational studies.¹⁷

Study design

DREAMY is a prospective, non-randomised, descriptive, multicentre cohort study. Following informed consent, patients undergoing general anaesthesia for obstetric surgery will be questioned about their experience of general anaesthesia, either in person or via telephone, using the Brice interview on three separate occasions within 30 days of anaesthesia. Patients who indicate possible memories during general anaesthesia will undergo structured follow up for up to 12 months. All patient reports will be analysed and adjudicated by a mixed-background expert panel, using a pre-defined classification for AAGA outcomes Fig. 1.

Setting

Patients have been recruited from participating hospitals in England during a 15-month recruitment window, beginning in May 2017. Between 40 and 60 hospitals are expected to participate.

Participants

Table 1 shows patient eligibility criteria. All urgencies of surgery (classified according to a model proposed by Lucas et al.¹⁸ and adopted by the Royal College of Obstetricians and Gynaecologist in the United Kingdom) are eligible, including emergency surgery.

Variables and measurement

AAGA will be identified using a four-stage approach:

1. Detection. Screening for AAGA will be performed with a structured Brice interview, adapted from the originally published form⁴ (Appendix 1) to incorporate categorical and open patient responses, maintaining consistency with use in several comparable studies.^{19,20} Since detection of AAGA may be increased by multiple repetitions of structured postoperative questioning,^{11,21,22} the Brice interview will be provided on three separate occasions over 30 days; 0–24 h postoperatively, 24–48 h and at 30 days. This approach is termed “Thrice Brice” and maximises the opportunity for participants

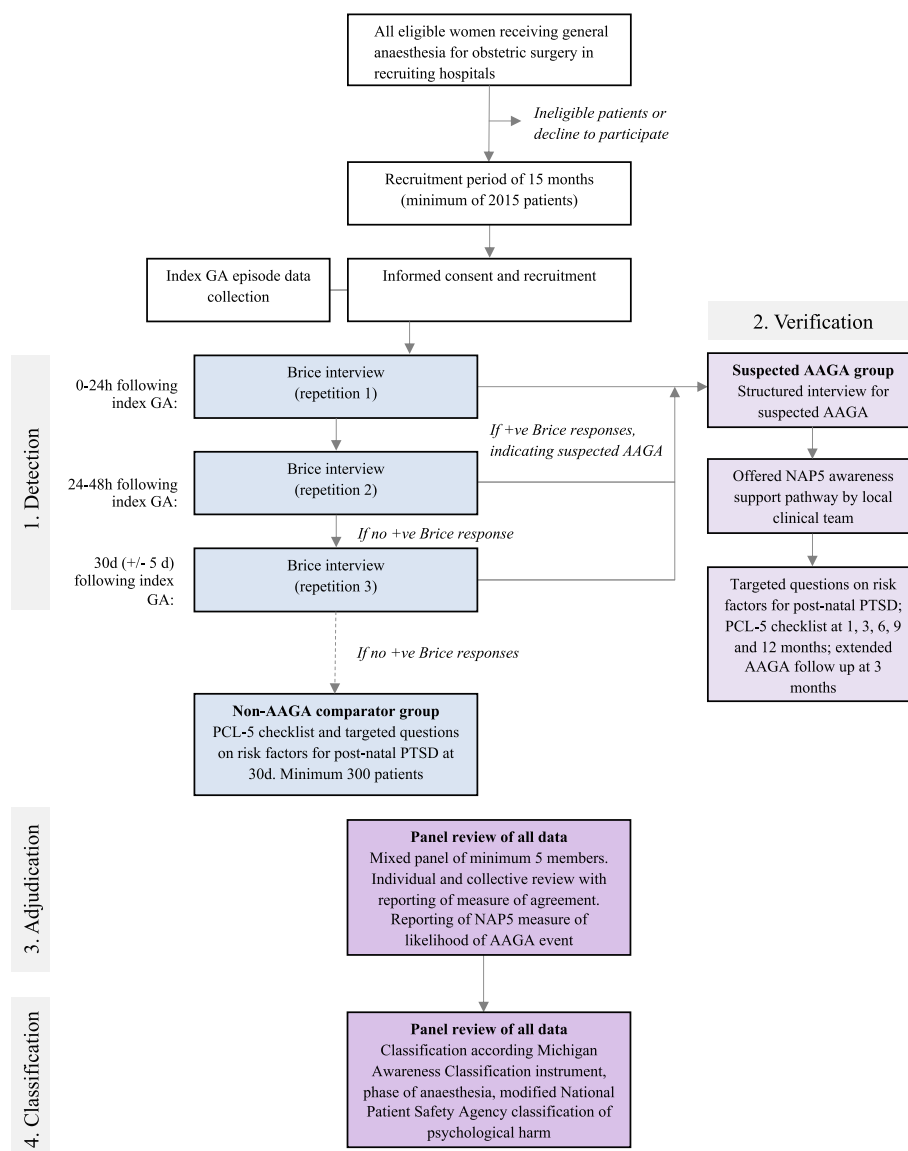


Fig. 1 Study design flow chart

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Adults (≥ 18 y and ≥ 24 weeks' gestation)	Patients confused or too unwell to complete the questionnaire
Received general anaesthesia (de novo or regional anaesthesia converted to general anaesthesia) for surgery with an obstetric indication. Eligible obstetric indication surgical procedures included, but were not limited to: caesarean delivery, manual removal of placenta, exploration under anaesthesia before or after delivery.	General anaesthesia for a non-obstetric surgical indication (e.g. colorectal or orthopaedic surgery in a pregnant patient)
Written informed consent obtained	Surgery ≥ 48 h postpartum Unable to communicate verbally or in writing in English language

to declare experiences recalled immediately following surgery (when the prospect for recall of detail is highest) and later emerging memories.

The first two questionnaires will be performed by local hospital investigators, offering the questionnaire but clarifying responses and answering queries in per-

son. The third Brice interview and all subsequent research follow up will be performed via telephone by the co-ordinating research team. Patients will be included for analysis even if fewer than three Brice responses are collected.

Any abnormal report indicating memories that a patient has attributed to the period between “going to sleep” and “waking up” will trigger a second, verification process to improve AAGA detection specificity.

2. Verification. To assure validity, data on AAGA reports will be collected using multiple methods. Patients reporting possible awareness will be independently interviewed by a study author, using semi-structured questioning to verify the detail, characteristics, plausibility and psychological response to the experience. Suspected AAGA structured interview schedules (Appendix 2) are adapted from the BAG-RECALL trial.¹⁹ Any specific description of events made in verification interviews will be checked with staff involved with clinical care to provide corroboration or refutation. This includes investigating the timing and specific nature of reported sensory perceptions.

All suspected AAGA patients will also be asked to complete a PCL-5 post-traumatic stress disorder (PTSD) checklist²³ by telephone at day 30, then 3, 6, 9 and 12 months following the anaesthetic episode. During first administration of the PCL-5 additional information will be obtained using a structured and multi-dimensional questionnaire on the patient’s self-reported mental health history, infant’s health status and psychological experiences in the gravidic-puerperal cycle. Question domains have been derived from recognised risk factors for developing PTSD during the postnatal period.²⁴ The PCL-5 symptom checklists will also be asked to a minimum comparator sample of 300 patients who have no indication of AAGA on “Thrice Brice” questioning.

An extended AAGA follow-up will occur at three months postoperatively, to investigate the nature of local clinical follow-up received by patients and how the AAGA episode has impacted on attitudes towards future anaesthetics and the postnatal experience.

3. Adjudication. Adjudication of patients’ reports according to the likelihood of each representing an AAGA experience will be performed by a panel of experts independent from study data collection and blinded to hospital site and any personal identifiers. Panel members will be drawn from both anaesthetists and psychologists, with prior understanding of AAGA, including individuals who adjudicated on NAP5 panels. A minimum of five panel members will review all reports.

Each panel member will first review the patient reports and anaesthetic episode data separately. Cases will be discussed collectively by the panel considering detail, plausibility and consistency of reported experiences with intra-operative process. Panel members will be reminded to be aware of “outcome bias” (where knowledge of the poor outcome can lead to a retrospective harsh judgement) and “groupthink bias” (where groups make potentially irrational decisions given a subconscious desire to agree with others). Panel members will declare separate adjudication decisions and the kappa statistic will be reported to measure agreement. Final allocations will be determined based on the majority adjudication decision of the panel.

AAGA reports will be graded according to a confidence scale adapted from NAP5 (Table 2).²⁵

4. Classification. The AAGA events will be graded by consensus opinion by the review panel in accordance with the Michigan Awareness Classification Instrument²⁶ (Table 3) and a modified version of the National Patient Safety Agency tool²⁷ adapted for NAP5 to be suitable for predominantly psychological harm related to AAGA (Table 4).¹

Where possible, events will also be classified according to the phase of anaesthesia (Table 5).

Table 2 Likelihood of a patient report representing accidental awareness during general anaesthesia (AAGA)

Likelihood that the report represents AAGA	Description
Certain/Probable	A report of AAGA in a “surgical setting” in which the detail of the patient story was judged consistent with AAGA, especially where report detail was verified independently or contained descriptions that would not otherwise be known to a patient
Possible	A report of AAGA in a “surgical setting” in which details were judged to be consistent with AAGA or the circumstances might have reasonably led to AAGA, but where otherwise the report lacked a degree of verifiability or detail
Unlikely	Details of the patient story were deemed unlikely or judged to have occurred outside of the period of anaesthesia
None	Evidence that the report was not AAGA or events occurred outside of the period of anaesthesia

Table 3 Michigan Awareness Classification (MAC) Instrument

MAC classification	Description
Class 0	No AAGA
Class 1	Isolated auditory perceptions
Class 2	Tactile perceptions (with or without auditory)
Class 3	Pain (with or without tactile or auditory)
Class 4	Paralysis (with or without tactile or auditory)
Class 5	Paralysis and pain (with or without tactile or auditory)

An additional designation of 'D' is applied where the report described distress during the experience (e.g. fear, suffocation, sense of impending death, etc.). AAGA: accidental awareness during general anaesthesia.

Table 4 Modified National Patient Safety Agency classification, including psychological impact on the patient, devised for use in NAP5

Severity	Revised definitions used in NAP5
0	No harm occurred
1	Resolved (or likely to resolve) with no or minimal professional intervention. No consequences for daily living, minimal or no continuing anxiety about future healthcare
2	Moderate anxiety about future anaesthesia or related healthcare. Symptoms may have some impact on daily living. Patient has sought or would likely benefit from professional intervention
3	Striking or long-term psychological effects that have required, or might benefit from, professional intervention or treatment. Severe anxiety about future healthcare and/or impact on daily living. Recurrent nightmares or adverse thoughts or ideations about events. This may also result in formal complaint or legal action (but these alone may not be signs of severity)
4	Caused death

NAP5: 5th National Audit Project in the UK and Ireland.

Table 5 Definitions used for phase of anaesthesia

Phase of anaesthesia	Description
Pre-induction	Defined as drug error before intended anaesthesia
Induction	Defined as the start of administration of a hypnotic drug with the intention of producing general anaesthesia. Cases in which there is a drug administration error during induction, resulting in failure to deliver a hypnotic agent, will be included as induction phase, since the anaesthetist's intention was to induce general anaesthesia irrespective of any drug error
Intra-operative	Defined as the period between skin incision and cessation of the administration of maintenance anaesthesia agents
Emergence	Defined as occurring after surgery has ended until a time when the patient feels awake and expects to be conscious. Emergence phase reports include residual neuromuscular blockade, but we will categorise uncomplicated "awake" emergence memories of extubation as non-AAGA, since delivery of anaesthesia has intentional ceased and the patient is expected to have sufficient return of consciousness and reversal of neuromuscular blockade for extubation
Other	Uncertain time

Statistical analysis

The minimum sample size was based upon confidence to detect an incidence of AAGA at least three times higher than described following Brice interviews in non-obstetric surgical patients. The assumption for the comparator proportion was based on data from the most recent study of AAGA in obstetric surgical patients.¹⁴ The baseline AAGA proportion was taken to be 0.15% (~1:666).^{5,6} An exact binomial test with a one-sided alpha of 0.05 showed that 2015 patients would be needed to give a power of 80% to detect a comparator proportion of >0.45%.

Commonly applied limits on alpha and beta error may yield poor precision estimates for the binomial proportion when rare events are expected. Likewise, disparity of AAGA detection and reporting may lead to under- or over-estimates of sample size power. On the basis that AAGA was expected to be a rare outcome in the sampled population and that the study had a descriptive objective (i.e. to describe the incidence of AAGA), no maximum sample size was pre-defined. Instead the study will use a combination of a minimum recruitment threshold with a descriptive approach, aiming to recruit a maximum number of eligible patients

during a 15-month recruitment period. The recruitment duration was selected pragmatically and feasibility was supported by an activity survey of obstetric general anaesthesia in hospitals expected to be involved in the study.

The primary outcome of proportion of obstetric patients reporting a composite of certain/probable and possible AAGA will be expressed using binomial confidence intervals and compared with established values using Fisher's exact or chi-squared testing. Analysis will be stratified for certain/probable and outcomes for other classification groups to provide optimistic or pessimistic confidence intervals for the estimated incidence of AAGA. Associations between anaesthetic, surgical and patient factors will be tested using univariate analysis. If sufficient AAGA events are identified, then a multivariate regression model will be used to evaluate the independent association of specific anaesthetic episode variables with AAGA, with results expressed as odds ratios. For secondary outcomes, data will be presented as: a number or percentage; mean and standard deviation for normally distributed data; and median and interquartile range for non-parametric data, with 95% confidence intervals.

The PCL-5 results will be expressed as a total symptom severity score (range 0–80) by summing scores from the 20 checklist items, and differentiated according to symptom criteria domains such as reliving, avoidance behaviour, emotional blunting and hyper-excitability.²⁸ The PTSD prevalence rates will be estimated for the entire sample and subgroups, including AAGA and non-AAGA patients. Results will be expressed with the respective 95% confidence intervals.

Case descriptions of the experiences of AAGA undergone by patients with AAGA will be presented in anonymised format. The phase of anaesthesia/surgery when the AAGA event occurred, alongside possible contributory, causal or mitigating factors, will be described where possible.

Anaesthetic episode data will be collected by local investigation from patient notes and anaesthetic records, before transferring to a central electronic database. Local clinical teams will maintain responsibility for provision of support to patients with AAGA. All sites will be encouraged to provide care in accordance with the NAP5 Anaesthesia Awareness Support Pack guidelines.²⁹

The DREAMY study is co-ordinated by a chief investigator, supported by a study steering group and an affiliated anaesthetic trainee network, the Pan-London Perioperative Audit and Research Network (PLAN). This network is led by anaesthetic trainees to benefit trainee learning and supports the development of resources to encourage large scale participation in multicentre studies of anaesthetic practice. Collaborations with regional anaesthetic trainee networks were invited.

Discussion

We present the DREAMY study protocol in order to demonstrate how the study has been designed to address challenges to the methodology and interpretation of AAGA research. The study combines approaches tested by NAP5 with direct questioning.

The first challenge relates to the nature of the outcome to be reported, as AAGA is a complex phenomenon. It occurs across a wide spectrum of experiences; descriptions of events are subject to variable interpretation by clinicians and researchers alike.³⁰ It is expected that only a minority of patients reporting AAGA will present clear evidence that can be corroborated, for example memory of specific intra-operative events or conversations between operating theatre staff. Since AAGA detection relies upon subjective reporting of a spectrum of experiences occurring in an unfamiliar hospital environment, a report indicating AAGA is likely to be unordered, misinterpreted, lacking in points of reference and potentially psychologically traumatic. The DREAMY protocol therefore includes varied approaches to enable detailed capture of patient reports. In addition, the 30-day postoperative interview is conducted by a trained interviewer who will be independent from each hospital, presenting an alternative route for disclosure. Training, guidance documents and advice regarding local communication and management of patients reporting distressing memories support patient wellbeing,²⁹ which may also improve conditions for reporting by patients.³¹

The second challenge is that AAGA can only be readily detected if memory of the experience is present. The relationship between memory and unintended consciousness during general anaesthesia is not necessarily straightforward. It is unknown how long a period of AAGA must last to produce a memory that can be recalled after waking from general anaesthesia; respondents in isolated forearm testing rarely have explicit recall afterwards.³² A minority of patients experiencing AAGA have no declarative memory of the event until several weeks postoperatively.^{5,33}

General anaesthesia affects perceptual and episodic memory formation at lower effect site concentrations than for hypnotic effects, inhibiting the communication pathways needed to translate memory from a short-term buffer ("working" memory) into explicit recall.³⁴ Hence, suppression of memory formation at anaesthetic concentrations that enable perceptive AAGA may interfere with the process that is fundamental to detection of AAGA.

Alternatively, memories of intra-operative events can be subject to recall bias or disruption by procedural factors. The timing and format of questions about memories are important. Best practices to identify AAGA reports are unknown, lacking validation of optimal

phrasing, timing and frequency of questions asked. Recall is a process of reconstructing rather than replaying a past event. Memories can be unreliable, or false memories be inserted, by encouraging patients to generate that information themselves.³⁵ Such outcomes tend to occur when patients are presented with repeated leading questions, a process that may potentially occur with the Brice interview.

Ultimately, credibility for AAGA outcomes relies on having the consistent, unbiased, detailed and contemporaneous records of patient memories following surgery. Whilst the Brice interview has face validity, construct and content validity are unquantified. Different variations in the delivery or phrasing of Brice questions have not been investigated. Comparisons between a single repetition of the Brice interview at postoperative day 28–30 and open-ended quality assurance interviews at postoperative day one have indicated higher detection of AAGA events using the Brice approach.²¹ Thus, Brice has become a de facto standard based upon commonality rather than any formal testing of validity.

The approach in the DREAMY protocol of three Brice interview repetitions over 30 days was designed to balance pragmatism with sensitivity in identifying transient memories and to minimise memory implantation. Although we acknowledge that there are limitations to Brice interviews, this methodology remains the only option to enable comparisons with previous studies. We consider Brice to be a sensitive tool for detecting AAGA, but lacking in specificity, hence the additional verification processes in DREAMY.

The third challenge relates to translating subjective descriptions of experiences into objective outcomes. The process of adjudication is often poorly reported with wide variation in blinded panel outcomes.³⁰ This finding may reflect inconsistency in study methodologies. The DREAMY protocol therefore employs a range of tools that have been tested by other studies, including the Michigan Awareness Classification Scale, the National Patient Safety Agency tool and PCL-5. We are also reporting intra-panel agreement to ensure transparency in the way in which AAGA reports are considered and outcomes structured.

The study design retains several limitations. The small number of anticipated AAGA events means that confidence intervals may remain wide. Patients with severely traumatic AAGA experiences may decline to consent for research participation, potentially introducing bias. However, this effect has not been described for previous (non-obstetric) patients. A minimum proficiency in English language potentially restricts participation in the study, but avoids the introduction of unknown bias from potentially inaccurate translation of patient reports.

In conclusion, DREAMY will provide vital descriptive data on AAGA incidence, experience and its

implications for obstetric patients. In addition, the study is expected to improve vigilance for AAGA in participating hospitals, to encourage adoption of recommendations on patient support from NAP5³⁶ and to raise the profile of an important patient-facing complication of anaesthetic practice. We urge others to improve and debate the methodological strategy used in DREAMY to establish and support standardised best practice for AAGA investigation.

Declaration of interests

Funding is via a National Institute of Academic Anaesthesia (NIAA) and Obstetric Anaesthetists' Association (OAA) research grant. Peter Odor was Chair of the Pan-London Perioperative Audit and Research Network (PLAN) from 2015 to 2018. Jaideep Pandit was the clinical lead for the 5th National Audit Project (NAP5). Nuala Lucas is an editor of IJOA and Chair of the OAA Education subcommittee, but was not involved in the editorial process for this manuscript. There are no other conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijoa.2020.02.004>.